

**REMARKS/ARGUMENTS**

***1. Status of the claims***

Claims 68-70 are added. Claims 48-49, 52-58, 62-70 are pending and under consideration with entry of this Amendment.

***2. Support for the Amendments***

Support for the amendments can be found in the specification, drawings and claims as originally filed. For example, claim 68 is merely the reinstatement of claim 59, which was inadvertently canceled. Claims 69 and 70 find support on, e.g., page 16, lines 23-26 of the specification. No new matter is added.

***3. Interview***

Applicants thank the Examiner for the helpful interview on August 19, 2003. It is Applicant's understanding from the interview that the only remaining rejection is under 35 U.S.C. § 112, first paragraph.

***4. Rejection under 35 U.S.C. § 112, first paragraph***

According to the Advisory Action mailed July 25, 2003, the specification requires fusion of the PR-1a signal sequence to Sarcotoxin 1a. The Examiner argues that statements on page 2, lines 18-22 and page 16, lines 13-17 indicate that "the PR-1a protein 'is required to stabilize the peptide.'" See Advisory Action. Based on page 16, lines 23-25 of the specification, the Examiner further argues that the PR-1a signal sequence is required. It is Applicants understanding that the Examiner does not question that other fusions or signal sequences could work, but that because the application allegedly states that the PR-1a protein (as fusion partner) and the PR-1a signal sequence is required, claims encompassing any signal sequence are too broad. Applicants respectfully traverse the rejection.

**A. The specification provides language that is not limited to a particular signal sequence or fusion partner**

While Applicants acknowledge the statements on page 2, lines 18-22 and page 16, lines 13-17 of the specification, it is also noted that the specification is drafted to encompass any signal sequence or fusion protein linked to Sarcotoxin 1a. For example, page 3, lines 30-31 states "the Sarcotoxin 1a is bound to a signal sequence of a plant protein." Indeed, original claim 7 uses the same language. There are no limitations to a particular signal sequence.

Similarly, the specification contemplated fusion with any plant gene. For example, page 4, lines 16-25 state that the invention includes plants transformed with a gene, wherein the gene "encoding an anti-bacterial peptide is bound to a plant gene via a hinge region of tobacco chitinase....." Page 9, lines 20-23 further states:

the term 'plant gene' as used herein refers to a gene of a plant. As the plant gene, any genes can be used. Preferably, examples of the plant gene include an pathogenesis related protein PR-1a gene of tobacco. However, the plant gene is not limited thereto.

In view of this language alone, it should be clear that the specification was not intended to be limited to a particular signal sequence or fusion partner.

**B. The application examples contradict any inference that a PR-1a fusion is required**

**i. The application does not state anywhere that the PR-1a signal sequence is required**

Applicants assert that the Examiner has wrongly interpreted page 2, lines 18-22 and page 16, lines 13-17 as indicating that the PR-1a signal sequence is required. There are no statements in the application that state that the PR-1a signal sequence is required. The statements if anything, state that fusion of Sarcotoxin 1a with the PR-1a protein (i.e., the entire protein) is "required," not fusion with the PR-1a signal sequence. Thus, it is improper to limit the Applicants to only the PR-1a signal sequence when in fact there is no such limitation in the specification.

The Advisory Action summarizes page 2, lines 18-22, page 16, lines 13-17 and page 16, lines 23-25 as follows:

Thus, the specification itself requires the presence of PR-1a as the signal sequence and PR-1a as the second protein (if present).

This is an incorrect reading of these sections of the specification. In fact, page 2, lines 18-22 and page 16, lines 13-17 state that fusion of Sarcotoxin 1a with the PR-1a protein, not the PR-1a signal sequence, is "required." Page 16, lines 23-25 read as follows:

Furthermore, a signal sequence of the tobacco PR-1a protein is added to an N-terminal of a fusion protein, whereby the fusion protein can be secreted.

This quotation does not state that any particular signal sequence is required. It merely states that the PR-1a signal sequence, like other signal sequences, facilitates secretion. Accordingly, the Examiner's conclusion that the application requires fusion with the PR-1a signal sequence in particular is wrong.

**ii. The examples demonstrate that a fusion with the PR-1a protein is not required**

Moreover, the statement that a fusion with the entire PR-1a protein is "required" is clearly at odds with the experimental data provided in the application. The examples demonstrate that the "PSP" construct, which is not a fusion with the PR-1a protein (*see*, Fig. 8), provides anti-fungal activity when expressed in plants. *See, e.g.*, page 32, lines 19-20 stating that PSP plants were resistant to *Pythium*. In view of the demonstration in the application that constructs not fused with PR-1a protein retain antifungal activity, it is clear that the Applicants have enabled those of skill in the art to construct active Sarcotoxin 1a expression cassettes without fusing Sarcotoxin 1a with PR-1. As the working examples contradict the statements made on pages 2 and 16, it is unreasonable to limit the Applicant to those statements in the specification.

Applicants note that new claims 69 and 70 are directed to those embodiments in which the PR-1a signal sequence is fused to Sarcotoxin 1a. It is Applicants understanding from the interview that these claims are allowable in view of the Advisory Action.

**C. A number of signal sequences were known as of the filing date of the present application**

While the application teaches that it is useful to secrete Sarcotoxin 1a into the extracellular space in plants, there is no basis for limiting the claims to a particular signal sequence. Nothing more than routine experimentation would be required of the skilled artisan to exchange the PR-1a signal sequence with another suitable signal sequence in order to construct a fusion protein as taught in the instant invention. As described in *Wands*, a “considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede.” *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982)). The courts have also repeatedly held that a “patent need not teach, and preferably omits, what is well known in the art” (*Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Company et al.*, 221 USPQ 481 (Fed. Cir. 1984)).

In fact, any signal sequence can be used to produce a fusion protein. Applicants refer the Examiner to the copies of the attached standard textbook pages (Buchanan *et al.*, (ed.) *Biochemistry & Molecular Biology of Plants* (2000), pages 178-183) in which signal peptides are discussed in detail. Although this textbook was published after the filing date of this application, as a tertiary reference, it is representative of what is generally know in the art about signal peptides. For instance, additional references cited in the textbook were published before the filing date of the instant application. On page 180 (section 4.5.3) of Buchanan *et al.* it is stated that signal peptides share important structural features and that the signal peptides of different secretory pathways are interchangeable, not only among plant proteins, but also among plant, animal, and yeast proteins. Hence, the art recognizes that there is no substantial difference in function from one signal sequence to the next. According to the text book (page 180; section 4.5.3), the presence of a signal peptide is sufficient to direct the secretion of a protein. Those of

skill in the art would reasonably predict that any signal sequence other than PR-1a could be substituted for the PR-1a signal sequence. There is no reasonable basis for the Examiner's assertions that only the PR-1a signal sequence could be used.

**D. The specification teaches how to overcome any enablement issues raised by Okamoto *et al.***

The Examiner cited Okamoto *et al.* as evidence that it is unpredictable what configuration of signal sequence, Sarcotoxin 1a and fusion partner will work to provide anti-fungal activity. *See*, Office Action mailed June 5, 2002 (paper no. 42), page 5. According to the Examiner, the lack of disease resistance of plants transformed with certain Sarcotoxin 1a/GUS fusions, as discussed on page 61, right column, second paragraph of Okamoto *et al.* demonstrates that it is unpredictable how to make active constructs using fusion partners.

Applicants assert that the specification teaches how to overcome such problems with fusion partners. The application teaches that steric hindrance with fusion partners can sometimes occur. The application suggests that use of a linker from the hinge region of the tobacco chitinase gene can be used to overcome this problem. *See, e.g.*, page 16, lines 1-6 and 18-23 of the specification. Using the application as a guide, those of skill in the art would have understood how to overcome the issues raised in Okamoto *et al.* by linking the fusion partner via a linker such as the hinge region to avoid steric hindrance. Indeed, the only claims that expressly recite fusion of Sarcotoxin 1a with a fusion partner are claims 53 and 62, each of which also recites fusing the partner via a hinge region.

Applicants note that the data in Okamoto *et al.* actually supports enablement of the present claims. The independent claims (48 and 58) do not require the presence of a fusion partner, but do include a signal sequence. As stated on the second paragraph in the right column of page 61 of Okamoto *et al.*, "[i]n ST10 plants, a considerable level of disease resistance was observed...." "ST10" plants are plants transformed with a signal sequence linked to Sarcotoxin 1a without a fusion partner. Thus the results of Okamoto *et al.* support enablement of the present claims.

**E. Summary**

The specification teaches that any signal sequence or fusion partner can be used according to the invention. Moreover, the examples demonstrate that PR-1a fusions are not required for anti-fungal activity, thereby contradicting any statements to the contrary. Furthermore, the specification does not state anywhere that any particular signal sequence is required for activity. The PR-1a signal sequence described in the specification and examples was merely used for convenience. Since a variety of signal sequences were known in the art as of the filing date, Applicants submit that it is improper for the Examiner to limit the claims to PR-1a signal sequence fusions. The claims are enabled for their full scope.

**4. References omitted in the last response are provided herein**

The Examiner indicated in the Advisory Action that the references cited in the previous Amendment were not submitted with the Amendment.

The references cited in the previous Amendment were as follows:

- A) Rouster *et al.*, *The Plant Journal* 11:513-523 (1997)
- B) Jiang *et al.*, *Plant Mol. Biol.* 30:679-684 (1996)
- C) Shah & Klessig, *The Plant J.* 10:1089-1101 (1996)
- D) Balandin *et al.*, *Plant Mol. Biol.* 27:1197-1204 (1995)
- E) Fisscher *et al.*, *Plant Mol. Biol.* 26:873-886 (1994)
- F) Carrasco *et al.*, *Plant Mol. Biol.* 21:1-15 (1993)
- G) Eyal *et al.*, *Plant Mol. Biol.* 19:589-599 (1992)
- H) Krebbers *et al.*, *Plant Mol. Biol.* 11:745-759 (1988)
- I) Buchanan *et al.*, (ed.) *Biochemistry & Molecular Biology of Plants* (2000),

pages 178-183.

For the convenience of the Examiner, Applicants have included the above-listed references.

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Amdt. dated July 25, 2003  
Amendment under 37 CFR 1.116 Expedited Procedure  
Examining Group

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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